Remarks

Claims 1-5 and 8-10 are currently pending in the application. Claims 6 and 7 were previously withdrawn as non-elected inventions.

Specification

The specification has been amended to perfect the applicants' priority claim (see 1. below). No new matter is added by these amendments.

Support for the Claim Amendments

The amendments to the claims are supported by the application as filed; no new matter has been added. Specifically, support for amending claim 1 to recite an immunogenic response induced in the lymph nodes draining the buccal mucous membrane region is found in the instant specification at page 7, lines 16-25, at page 1, lines 12-17, and page 10, line 24-page 11, line 5, together with the table following beginning at page 17.

Perfected Claim for priority under 35 U.S.C. 119(a) based on FR/98/08354

The priority claim to international application PCT/FR99/01554 was incorrectly listed in the originally-filed Application Data Sheet as a foreign application. As this international application designated the United States of America, priority as a CIP under 35 U.S.C. § 120 or 365(c) is proper. The enclosed petition and Supplemental Application Data Sheet seek to correct this clerical error. Priority was properly claimed in the inventors' Declaration (previously submitted). Applicants respectfully request entry of a corrected Application Data Sheet, appended herewith together with a Petition for entry of the corrected paper.

The foreign priority document upon which the applicants have based their 35 U.S.C. 119(a) priority claim is French application number 98/08354 which had a filing date of 26 June 1998. The international application from which the applicants claim priority is PCT/FR99/01554 filed 28 June 1999. The PCT application correctly claimed priority from FR98/08354 because June 26 1999 was a Saturday, and therefore a filing date of Monday, 28 June 1999 is deemed filed within twelve months from the date on which the foreign application relied upon for priority was filed. Applicants respectfully request that the Examiner acknowledge the priority claim to the instant application.

Withdrawal of prior objections to claims and specification, and prior rejections of claims under 35 U.S.C. 112, and 35 U.S.C. 102

Applicants thank the Examiner for withdrawal of prior objections of claims and specification, and prior rejections of claims under U.S.C. 112, and 35 U.S.C. 102.

Rejection of claims 1-3, 5 and 8-10 under 35 U.S.C. 103(a)

The Examiner has rejected claims 1-3, 5 and 8-9 in their newly amended form, and new claim 10 as being unpatentable under 35 U.S.C. 103(a) over Thibodeau et al, in view of Lowell et al. (U.S. patent 5,985,284) and Heiber et al. (U.S. Patent 5,516,523). Applicants respectfully disagree for the following reasons. The Examiner appears to argue that it would have been obvious to combine the references to arrive at a method of administering an immunogen to the floor of the mouth. But the instant claims are not simply that. They recite a particular class of immunogens (*i.e.*, those of pathogens having a gateway into the buccal mucous membrane) to achieve a particular result (induction of a local and systemic IgA response). The Examiner appears not to even have alleged that the prior art teaches these elements, let alone specifically identified where in the art they are taught.

The Examiner states that administering a liquid to the mouth would inherently result in the liquid contacting the floor of the mouth. The applicants respectfully disagree. Whether the liquid would contact the floor of the mouth would depend in large part on how much liquid was administered and the location within the mouth of the administration. For example, a small amount of liquid administered to the back of the tongue would seem unlikely to reach the floor of the mouth. The reference referred to by the Examiner teaches that the liquid was administered drop-by-drop, *i.e.*, in small amounts, and fails to identify where in the mouth it was administered. The applicants respectfully submit that one cannot conclude that any liquid necessarily reached the floor of the mouth.

Furthermore, while Heiber mentions the floor of the mouth as part of the sublingual mucosa, neither this reference nor any of the other prior art suggests the floor of the mouth in particular, let alone the administration to that site of an immunogen having a gateway to the buccal mucosa and the resultant local and systemic IgA response.

Nor does Heiber or any of the art suggest targeting the buccal mucosa (the lining of the cheek) by administration not to the buccal mucosa, but to the floor of the mouth (in the sublingual mucosa).

Applicants respectfully assert therefore that there is no reason from Heiber's or Lowell's teachings to administer an immunogen having a gateway to the buccal mucosa by administration via the floor of the mouth.

While Thibodeau et al. discloses a topical application of HIV gp160 to the oral mucous membranes of rabbits and mice, it is only via booster injections, intraperitoneally and intramuscularly, that a systemic response is obtained (see Thibodeau et al. at page 390).

Furthermore, Thibodeau differs in two other ways. Thibodeau et al. does not teach or disclose administration to the floor of the mouth, only administration that is oral. The concept of targeting the buccal mucosal gateway with an agent for that gateway is entirely absent, as is the case for the other references cited by the Examiner.

Second, there are no grounds for applying results in rabbits to humans. See the instant specification at page 2, lines 22-32. The Examiner has stated in the paragraph bridging the Office Action, pp. 6-7, that the applicants have provided no support in the specification or otherwise for the assertion that the results in rodents cannot necessarily be transferred to primates. However, as we noted in the full paragraph on p. 6 of our February 4, 2004, response, the applicants attested (because they signed the Declaration) in the specification that "there are no grounds for saying that the results [seen in rabbits] can be applied to humans." Furthermore, the Examiner has provided no scientific basis for asserting to the contrary, *i.e.*, that the results in rabbits *are* applicable to humans.

Lowell et al.'s teaching of the sublingual mucosa adds no further motivation beyond Heiber et al., for the reasons stated above. The Examiner states and apparently places much weight on the assertion that Lowell teaches that sublingual administration of an immunogenic composition would be effective in humans. But the instant claims do not recite merely sublingual administration to primates, they recite administration to the floor of the mouth an immunogen specific for a pathogenic agent having a gateway into the buccal mucous membrane (*i.e.*, not just any immunogen) with the result that a local and systemic IgA response is induced. Neither Lowell nor the other art teach these additional elements of the claim.

Applicants respectfully assert therefore that there are no grounds for combining Lowell et al. and Heiber et al., with Thibodeau et al.

Lastly, there is simply no basis in the cited art for one of ordinary skill in the art could reasonably infer that both a local and systemic response could be achieved by administration to the floor of the mouth of an immunogen specific for a pathogenic agent having a gateway into the buccal mucous membrane.

Applicants therefore request that this rejection be withdrawn.

Rejection of claims 1-3, 5 and 8-10 under 35 U.S.C. 103(a)

The Examiner has rejected claims 1-3, 5 and 8-10 as being unpatentable under 35 U.S.C. 103(a) over Thibodeau et al, in view of Mathiowitz et al. (U.S. Patent No. 6,235,313), and Irwin et al. (U.S. Patent No. WO 96/20731), the applicants again traverse the rejection, essentially for the same reasons given above. Mathiowitz teaches a topical administration, a teaching which does not provide either a motivation to try, or an expectation of success in trying, administering an immunogen into the floor of the mouth such that drainage to the lymph nodes will occur to produce a systemic as well as local response. Applicants also traverse with respect to the Examiner's use of Irwin et al. as a reference because, as explained in 3, above, there is no suggestion that the lymph nodes could be targeted by oral administration and thus no grounds for combining these references. Applicants therefore request that this rejection be withdrawn.

Rejection of claims 1-3, 5 and 8-10 under 35 U.S.C. 103(a)

The Examiner has rejected claims 1-3, 5 and 8-10 as being unpatentable under 35 U.S.C. 103(a) over Thibodeau et al, in view of either Lowell et al. (J. Infec. Dis. 175: 292-301), or Gandhi et al. (Adv. Drug Deliv. Rev., 13: 43-74). The applicants respectfully traverse for same reasons asserted above. The mere delivery of preparations to the oral cavity, even to the oral mucosa, does not provide either a motivation to try, or an expectation of success in trying, administration of an immunogen specific for a pathogenic agent having a gateway into the buccal mucous membrane into the floor of the mouth such that drainage to the lymph nodes will occur and a systemic as well as local response is produced. Applicants therefore request that this rejection be withdrawn.

Rejection of claims 1-3, 5 and 8 and 9 under 35 U.S.C. 103(a)

The Examiner has maintained his rejection of claims 1-3, 5 and 8-10 as being unpatentable under 35 U.S.C. 103(a) over Hinkula et al, (Vaccine 15: 874-878) in view of Irwin et al., and Beckenkamp et al. (HNO 33:196-203), and further in light of Kozlowski et al. (Infect. Immun. 65(4): 1387-94), and Gorse et al. (Clin. Diag. Lab. Immunol. 3(6):769-73) Applicants again respectfully traverse for the reasons given above. Hinkula's teaching, specifically "in the oral cavity by intranasal, tongue injection, Accell device [a form of epidermal injection often used for the stomach], or dental injector" merely suggests inducing mucosal immunity in the oral cavity via these approaches, and lacks any motivation alone or in combination with other cited references to specifically administer to the floor of the mouth a immunogen of a pathogen having a gateway for the buccal mucosa. Applicants continue to assert the lack of any motivation to try an alternative oral route over injection into the tongue or gums of mice in view of Hinkula's teaching that mucosal immunization at gastrointestinal or respiratory sites, particularly the intranasal site may be far more effective (see Hinkula at page 877, right column).

Even in combination with the additional references cited by the Examiner, it cannot be said that Hinkula motivates one to contemplate the specific region of the mouth. While Gorse et al. affirms that the production of secretory IgA antibodies is an important factor in effective vaccination against sexually transmitted disease, it is not an obvious step to combine such an observation with the teaching of Hinkula. Both Gorse and Hinkula lack any suggestion or motivation to use an immunogen specific for a pathogenic agent with a gateway into the buccal mucous membrane region. Similarly, while noting that immunogenic delivery is possible by oral sublingual administration, Irwin et al. does not distinguish the floor of the mouth, nor does it mention the critical factor of producing secretory IgA antibodies. None of the teachings suggest the floor of the mouth specifically, the use of an agent against a pathogen with a gateway into the buccal mucous membrane region, or a local and systemic IgA response thereby induced. Therefore, the applicants assert that the instant claims are not obvious over Hinkula et al. in view of Beckenkamp et al. and Kozlowski et al., Gorse et al., and request that this rejection be withdrawn.

Rejection of claims 1-3, 5 and 8-10 under 35 U.S.C. 102(e)

The Examiner has rejected claims 1-3, 5 and 8-10 as being unpatentable under 35 U.S.C. 102(e) over Becker et al., (U.S. Patent No. 6,379,675) et al, or in the alternative under 35 U.S.C. 103(a) as obvious over Becker et al. in view of Gorse and Beckenkamp. Becker cannot be said to anticipate the instant claim 1 to the use of an agent "having a gateway into the buccal mucous membrane." The applicants respectfully assert that Becker is at best claiming the genus of orally administered vaccines with no suggestion of or motivation to use an immunogen specific for a pathogenic agent with a gateway into the buccal mucous membrane region. Nor is there any reason to target the floor of the mouth as a result of combining Becker's teaching with the teaching of the remaining references suggested by the Examiner for the reasons asserted above. Applicants respectfully assert therefore that these rejections be withdrawn.

Conclusion

In view of the foregoing, the applicant respectfully requests reconsideration and withdrawal of the pending § 102, and § 103 rejections. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

Date: June 18, 2004

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